IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE: NATIONAL PRESCRIPTION OPIATE LITIGATION This document relates to: *The County of Summit, Ohio, et al. v. Purdue Pharma L.P., et al.* Case No. 18-op-45090 and *The County of Cuyahoga v. Purdue Pharma L.P., et al.* Case No. 1:18-op-45004	MDL No. 2804 Hon. Judge Dan A. Polster

MEMORANDUM IN SUPPORT OF DEFENDANTS' MOTION TO EXCLUDE EXPERT TESTIMONY OF KATHERINE KEYES, ANNA LEMBKE & JONATHAN GRUBER RE THE "GATEWAY HYPOTHESIS" OF CAUSATION

Defendants manufacture and/or distribute prescription opioid medicines, which have been and/or continue to be approved by the FDA as a medically appropriate option for healthcare providers who make medical judgments about how to treat patients with pain. These medicines have always been regulated by DEA and carry FDA-required warning labels regarding the known potential risk of addiction. The two counties who are suing Defendants acknowledge that the public health problem they face now arises primarily from the abuse of drugs that Defendants have never manufactured, distributed or sold—street drugs such as heroin and illicit fentanyl,

often introduced into the country by foreign criminal cartels, international drug traffickers and local gangs.[1]

How do Plaintiffs purport to hold Defendants—the manufacturers and distributors that supply FDA-approved prescription opioids—responsible for all of the governmental costs that they claim now attend the abuse of these illegal street drugs? The answer is, by their own admission, nothing but a hypothesis—specifically the "gateway" hypothesis. This unproven idea, as applied here by three of Plaintiffs' experts, posits that the entire problem of illicit heroin and fentanyl use today was somehow "caused" by the last almost quarter century of trained healthcare providers prescribing legal opioid medicines. The attenuated "link" Plaintiffs attempt to make between Defendants' legally marketed and prescribed products and the use of illicit drugs sold by criminals is both too speculative and unreliable as a matter of science, and too remote as a matter of law. This is a textbook example of where a Court's exercise of its gatekeeping role, conferred by *Daubert* and Rules 702 and 403, is critical to ensure that no jury bases its decision on such unsubstantiated, misleading and prejudicial evidence.

I. PLAINTIFFS' GATEWAY HYPOTHESIS

In an attempt to establish a causal connection between the Defendants' legal opioid medications and distribution practices and the illegal heroin and fentanyl trade, Plaintiffs proffer the testimony of three experts—Anna Lembke, M.D.[2], Katherine Keyes, Ph.D.[3], and Jonathan

[1] *See*, e.g., Ex. 1, 2016 Cuyahoga County Opiate Task Force Report ("Heroin and fentanyl are at the forefront of this epidemic") (CUYAH_14194735, at -736).

[2] Lembke is Associate Professor, Chief of the Addiction Medicine Dual Diagnosis Clinic, Medical Director of Addiction Medicine, and Program Director of the Addiction Medicine Fellowship, in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine.

[3] Keyes is Associate Professor of Epidemiology at Columbia University.

Gruber, Ph.D[4] ("the Experts" or the "Three Experts"). All three assert that use of prescription opioids, *including* use by patients who have been appropriately prescribed opioids by a licensed physician, leads to heroin use. Each is an agent. Each is an agent through which Plaintiffs will tell the jury to hold Defendants responsible for a societal problem today that is many steps removed from any product Defendants ever manufactured or distributed.

Dr. Lembke claims to have identified "a clear link" between "exposure" to prescription opioids and "the subsequent use of heroin and other illicit opioids." She further claims that "the major increase in prescription opioid use ***beginning in the late 1990s*** has served as a gateway to increased heroin use …."[5] At her deposition, Dr. Lembke specifically posits the "Gateway Effect"—namely, how hypothetical prescribed patients under the care of a hypothetical licensed physicians, who then hypothetically retire or get ill or otherwise stop prescribing, could hypothetically go on to ultimately abusing heroin and illicit fentanyl.

> [T]he group I'm referring to in the Gateway Effect is … those individuals who started with a medical prescription and then became addicted through that medical prescription ….
>
> [***I***] ***posit an individual who began with a prescription of an opioid from a doctor***.
>
> * * *

[4] Gruber is Professor of Economics at the Massachusetts Institute of Technology.

[5] Lembke Report at 84. (The reports of Lembke and Keyes are attached to the brief in support of Defendants' Motion to Exclude the Marketing Causation Opinions of Mark Schumacher, Anna Lembke, and Katherine Keyes. The report of Gruber is attached to the separate motions to exclude his testimony.)

For purposes of this memorandum, (i) all emphases are added unless otherwise noted, (ii) internal quotations are omitted, and (iii) the different problems of heroin and illicit fentanyl abuse are referred to as "heroin abuse" for the sake of brevity.

> And eventually that individual … has neurologic changes in their brain such that …they begin to experience withdrawal often between doses ….
>
> And again, the compassionate doctor … continues to escalate until that individual is at a very, very [*sic*] dose and that individual spends almost all their time possibly going to the emergency room to get opioids to help with their worsened pain and their withdrawal …
>
> Now, should it happen that … that doctor retires or that doctor gets ill and can't treat that person anymore or that individual moves to another region or the doctor moves to another region and ***then that individual can no longer obtain the opioids through the prescription*** …, ***then sometimes individuals will look to alternative and illicit sources of opioids***.[6]

Based on this hypothetical scenario regarding what a legitimate patient could possibly experience (presumably because all opioid medicines are known to have addiction potential and are so labeled), she then assigns the entire problem of heroin and illicit fentanyl today to Defendants in the aggregate and the manufacture, marketing and sale of their products going back decades. She sweeps in among those allegedly "caused" to abuse heroin a broad and undifferentiated universe including people who may have never previously used a prescription opioid—either legitimately by prescription or illegitimately; people who previously used other drugs, such as crack cocaine; and people who may have experimented with a host of drugs.

Dr. Keyes opines that "[p]rescription opioid use is causally related to heroin use,"[7] such that all Defendants can be held jointly liable for today's illicit opioid problem in its entirety. But she remains studiously vague regarding whether "prescription opioid use" is focused on prescribed pain patients or whether it includes those who may have used an opioid obtained

[6] Ex. 2, Lembke Dep. 80, 82–85, 90–94.

[7] Keyes Report 25.

without a prescription, by diversion or through some other improper means. Whatever "prescription opioid users" might mean to Dr. Keyes, she admits that "the proportion of prescription opioid users who progress to heroin use is ***relatively small***," but she still claims they "can explain the ***majority of increases in heroin in the United States***."[8]

Dr. Gruber offers the "gateway" hypothesis as one piece of his overall opinion that "[t]here is a direct, causal relationship between defendants' shipments of prescription opioids and the misuse of and mortality from illicit opioids, including heroin and fentanyl."[9] That opinion includes "prescription opioids that are used both for medical purposes and those that are not used for medical purposes."[10] Like Dr. Lembke and Dr. Keyes, he reviewed the epidemiologic literature and determined that studies "establish[] the link" between prescription opioids and heroin use[11]—though unlike Dr. Keyes, he admitted that the studies themselves "do not prove a causal relationship to the standards that we use in economics literature."[12]

Important to appreciating the gateway-hypothesis testimony of the paid litigation Experts on which Plaintiffs rely is the pre-litigation published opinion of the counties' own non-retained mixed fact/expert witnesses, the Cuyahoga Medical Examiner Dr. Gilson. In a 2014 review of "The Cuyahoga County Heroin Epidemic," Dr. Gilson wrote that "there is a dearth of firm

[8] *See, e.g.*, Keyes Report at 3 (emphasis added).

[9] Gruber Report at 9.

[10] Ex. 3, Gruber Dep. 60:11–21.

[11] Gruber Report at 62.

[12] Ex. 3, Gruber Dep. 333:20–334:6.

evidence establishing the role of OPR [opioid pain relievers] as a gateway to heroin."[13] While Dr. Gilson noted a "link" between persons using OPR and heroin deaths he admitted that "it is unclear whether this represents evidence of a transition between OPR and heroin or simply reflects an addict population that uses these substances interchangeably."[14]

The Three Experts' "gateway" opinions should be excluded for three reasons. First, there is no scientific evidence that even purports to look at—let along find a causal link between—properly prescribed pain patients and today's heroin and fentanyl problems. The Experts cite no studies that connect these two populations (legitimate medical users of prescription opioids and illicit drug users), because there are none. Second, even the studies the Three Experts cite—which all look at known "non-medical users," functionally abusers, of prescription opioids—do not claim that heroin or fentanyl use is "caused" by such prior non-medical use or abuse of prescription opioids in this population. Third, Plaintiffs' "gateway" hypothesis—beyond being speculative—simply does not "fit" within any recognized legal framework for this case and is, frankly, a bridge too far. Nothing in the law comes close to allowing Plaintiffs to recover damages against a large and diverse group of lawful businesses, not for any harm caused by products they controlled, but rather by products that are illegal, put into the stream of commerce by others, and used by people who surely know they offer no medical benefit and only can cause harm. Plaintiffs cannot simply ignore all of the societal reasons why patterns of drug abuse and misuse change over time for the convenience of pinning liability for these costs on Defendants.

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[13] Ex. 4, Thomas Gilson et al., *The Cuyahoga County Heroin Epidemic*, American Forensic Pathology (Mar. 1, 2014).

[14] Relatedly, county fact witness Deborah Forkas, the former director of Childrens' and Family Services for Cuyahoga County was asked "Do you know any of the data about when people end up dying of heroin or fentanyl … what the actual data shows on how those people are getting started with their addiction?" Her answer was "Marijuana." Ex. 5, Forkas Dep. 248:1–8.

II. THE LEGAL STANDARD

Defendants will not restate the general legal principles that are set out in detail in the "roadmap" brief submitted simultaneously. It bears emphasis, however, that it is a well-established *Daubert* principle that an expert may not render an opinion that A causes B when the studies on which she relies stop short of drawing that conclusion. In *General Electric v. Joiner*, 522 U.S. 136, 141 (1997), the Supreme Court elaborated its *Daubert* analysis in affirming exclusion of expert medical causation testimony that the plaintiff's cancer was caused by exposure to PCBs. The Court said that an expert may not rely upon a study to support a causal finding that is not supported by the study's authors. In *Joiner*, the Supreme Court held that where the authors of an epidemiological study "were unwilling to say that PCB exposure had caused cancer among the workers they examined, their study did not support the experts' conclusion that [plaintiff's] exposure to PCB's caused his cancer." *Id*. at 145. "It is axiomatic that ***causation testimony is inadmissible if an expert relies upon studies or publications, the authors of which were themselves unwilling to conclude that causation had been proven***." *Huss v. Gayden*, 571 F.3d 442, 459 (5th Cir. 2009); *accord Happel v. Wal-Mart Stores, Inc.*, 602 F.3d 820, 826 (7th Cir. 2010). An opinion that goes beyond the evidence in that way does not meet *Daubert*'s "reliability" requirement.

Of course, "in order to qualify as 'scientific knowledge,' … [p]roposed testimony must be supported by appropriate validation—*i.e.*, 'good grounds,' based on what is known." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 590 (1993). To be sure, "the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F. 3d 316, 319 (7th Cir. 1996).

Plaintiffs' "gateway" hypothesis must be excluded because—even putting aside the host of particularized criticisms one could offer about the lack of reliability with the data they cite—

the bottom line remains that their opinion is still no more than a hypothesis. It is not—by any means—something any credible scientists has ever claimed is established as cause and effect.

III. THERE IS NO RELIABLE SCIENTIFIC EVIDENCE THAT MEDICAL USE OF PRESCRIPTION OPIOIDS BY PAIN PATIENTS IS THE CAUSE OF HEROIN ABUSE TODAY

Each of the Experts, in stating the "gateway" hypothesis, claim that "prescription opioid use" (not defined to clarify whether this means prescription opioid use for patients with legitimate prescription or those people who obtain prescription opioids illicitly from friends, family members, or drug dealers) leads to heroin abuse. But, at deposition, Dr. Lembke made clear that she is specifically "postulating" a trajectory from prescribed pain patient to illicit drug user and that her opinion is focused on these individuals as the "cause" of today's heroin and illicit fentanyl problems. There is no evidentiary basis from which Dr. Lembke or any expert may reliably conclude that there exists a cause and effect relationship between medical prescription opioid use and today's problem of heroin abuse in these counties. Indeed, none of the Three Experts identifies a single study that was designed to answer—or in any way purports to answer—the question whether patients who are prescribed opioids under medical supervision transition to heroin or fentanyl use in any numbers that could meaningfully explain today's challenges, or that concludes that such "transitioning" is caused by their prior medical use of a prescription opioid.

Dr. Lembke (like Dr. Gruber) relies on a small subset of the same "evidence" as Dr. Keyes who, for her statement that "[p]rescription opioid use is causally related to heroin use,"[15]

[15] Keyes Report 25. Dr. Lembke cites four of these studies, and Dr. Gruber, five. Lembke Report at 84–85 nn. 341–46; Gruber Report at 63–66 nn. 100–117.

relies on 16 epidemiological articles[16] that make observations regarding the potential association not between non-medical use of prescription opioids and heroin use. None of these articles reports on a controlled clinical trial designed to answer the hypothesis (or any hypothesis) the Experts put forth. All are observational and suffer from a myriad of limitations and potential confounders that affect their reliability. But even absent those challenges, the bigger problem with them is that they all describe individuals who engaged in ***non-medical use*** of prescription opioids.[17] While Plaintiffs seek to make the Court and jury believe they can establish that legitimate opioid use pursuant to a doctor's prescription is the cause of heroin abuse, the epidemiological evidence on which the experts rely tests a ***different*** hypothesis and involves a different path—the path from prescription opioid ***abuse*** to heroin abuse.

There is no dispute that the 16 articles concern non-medical prescription opioid abuse, not legitimate medical use. The articles say so, and Dr. Keyes so describes them. The most recent of those studies—authored by Dr. Wilson Compton of the National Institute of Drug Abuse—was published in the New England Journal of Medicine in 2016.[18] Dr. Compton is clear that existing studies involve prior ***non-medical*** use of prescription opioids: in surveying the literature, he uses the term "non-medical" 15 times to describe the use of prescription opioids that preceded heroin abuse (where "non-medical" use is defined as "using medications that were not prescribed for [the user] or were taken only for the experience or feeling that they

[16] Keyes Report 26 ("I reviewed 16 studies …"). To be precise, she cites 16 articles, not all of which are studies.

[17] Such non-medical use is referred to in the scientific literature as non-medical pain reliever (NMPR) or non-medical prescription opioid use (NMPOU).

[18] Ex. 6, Wilson M. Compton et al., *Relationship between Nonmedical Prescription-Opioid Use and Heroin Use*, N. Engl. J. Med., 374, 156–57 (2016) (hereinafter "Compton").

caused.").[19] Dr. Keyes's report says, "I reviewed 16 studies that found that individuals who use prescription opioids ***non-medically*** have higher rates of injecting and snorting heroin …."[20] And Dr. Catherine Rahilly-Tierney, an epidemiologist and expert designated by Cardinal Health, McKesson Corporation, and AmerisourceBergen Drug Corporation,[21] reviewed the same studies and said, "All of these studies enrolled adults with preexisting NMPOU or abuse of illicit heroin."[22] She found "***no studies*** that examined incident heroin initiation among patients with pain who are prescribed opioid analgesia."[23]

In short, none of the three experts proffered by Plaintiffs who opine on the "gateway" hypothesis has offered a single study that even tests—let alone supports—the hypothesis that medical use of prescription opioids causes the abuse of illicit street drugs, and their belief otherwise is speculation. *Daubert* clearly instructs, however, that "a key question to be answered in determining whether a theory … is scientific knowledge … will be whether it can be

[19] Ex. 6, Compton at 154.

[20] She makes this point about both those studies that involved adolescents ("I cited above the evidence among adolescents and young adults that has found strikingly high estimated incidence rate ratios for the transition to heroin given ***non-medical*** prescription opioid use …") as well as those studies that involved adults ("There are also numerous studies that demonstrate strong relationships between ***non-medical*** prescription opioid use and heroin use among adults"). Keyes Report at 26.

[21] Dr. Rahilly-Tierney is an Associate Epidemiologist at Brigham & Women's Hospital, an Instructor in Medicine at Harvard Medical School, Assistant Professor in Medicine at Boston University, and a staff physician at VA Boston Healthcare System.

[22] Ex. 7, Rahilly-Tierney Report 21. Of the 16 articles cited by Keyes, five either contained no quantitative data or contained insufficient data to tell which came first—the use of prescription opioids or the use of heroin.

[23] *Id*. *See* Ex. 8, Report of Dr. Robin Lyerla 2 (Plaintiffs' "gateway" hypothesis "largely relies on retrospective studies, which suggest association, not causality."). Dr. Lyerla is an epidemiologist for Mallinckrodt, Endo, Janssen, Purdue, Teva, and Allergan.

(and has been) tested." 509 U.S. at 593. The law also bars "subjective belief or unsupported speculation." *Id.* at 590. Thus, a court should exclude expert testimony "that is connected to existing data only by the *ipse dixit* of the expert." *Joiner*, 522 U.S. at 146. *Baker v. Chevron USA, Inc.*, 680 F. Supp. 2d 865 (S.D. Ohio 2010), is instructive. There, plaintiffs' experts relied on studies finding that exposure to high levels of benzene caused illnesses to conclude that plaintiffs' exposure to lower levels of benzene caused their illnesses. *Id.* at 887–88. The court excluded the testimony because the analytical gap between the cited studies and plaintiffs' expert opinions, including their causation theory, was too great, *see id.* at 882 n.13, and the Sixth Circuit affirmed. 533 F. App'x 509, 520–21 (6th Cir. 2013). Likewise, the Experts' "gateway" opinion must be excluded as unreliable under *Daubert*.

IV. THERE IS NO RELIABLE EVIDENCE THAT NON-MEDICAL "USE OF PRESCRIPTION OPIOIDS" IS THE CAUSE OF HEROIN ABUSE TODAY

Even if the Three Experts' "gateway" hypothesis were limited only to non-medical users of prescription opioids, there would still be no method reliable under *Daubert* by which they could conclude that non-medical prescription opioid use ***causes*** heroin abuse.

Regarding the nature of the association between prior non-medical use of prescription opioids and later heroin abuse, Dr. Compton's 2016 article says:

> Studies that address the patterns of heroin use in nonmedical users of prescription opioids are mostly observational and descriptive (i.e., nonexperimental). Thus, ***conclusions about cause and effect are uncertain***. Yet, certain consistent findings of a positive association between nonmedical use of prescription opioids and heroin use are highly suggestive and plausible ….[24]

Dr. Keyes does not disagree. She does not claim that the any of the studies on which she relies find a cause-and-effect association between (even) non-medical use of prescription opioids

[24] Ex. 6, Compton 156.

and heroin abuse, let alone legitimate medical use of prescription opioids and heroin abuse. Asked to acknowledge that "none of the articles that you cite conclude that there is a causal relationship between prescription opioid use and heroin use," she dodged the question, answering that "[a]ny one particular study doesn't make that case, it's the body of evidence."[25]

But Dr. Compton considered the body of evidence, and did so in a review article published in the New England Journal of Medicine, where he stated that any "conclusions about cause and effect" that could be drawn were "uncertain." And appropriately so. "Generally, researchers are conservative when it comes to assessing causal relationships, often calling for stronger evidence and more research before a conclusion of causation is drawn." *Reference Manual on Scientific Evidence* 599 (3d ed. 2011). And, of course, *Daubert* requires that "an expert, whether basing testimony upon professional studies or personal experience, employ in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). But when asked specifically about the Compton article, Dr. Keyes throws scientific caution to the wind:

> Q. If you were writing for a professional journal would you draw a conclusion about causality from the observational studies that Dr. Compton looked at?
>
> A. So I do write for professional journals. And I have evaluated the literature in this report. And I would draw the conclusion in any forum, that the available literature is consistent with a causal association. I mean, even Wilson Compton in this sentence said that, "It's highly suggestive and plausible given their common pharmacologic principles." ***I think I would go a step further given that we now have three more years of data since this was published***.[26]

[25] Ex. 9, Keyes Dep. 260–61.

[26] Ex. 9, Keyes Dep. 304–305.

First, note that Dr. Keyes acknowledges that, in giving her opinion that there is a causal relationship, she is going "further" than Compton (or anyone else). Second, note that her justification for going "further" is not that Compton misunderstood the existing studies, but that "we now have three more years of data" (a rationale she gives twice).[27] Her report does not cite any data from 2016–2019, nor does she cite any study, article or data that post-dates the 2016 Compton article.[28] Third, also note that Dr. Keyes does not claim there is a cause-and-effect relationship, only that the literature is "consistent with" a causal association. The two are not synonymous. As the Sixth Circuit has observed, to say that something is "'consistent with causing'" an effect is to "testify to a possibility rather than a probability." *Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349, 1360 (6th Cir. 1992). For an expert opinion about causation to be "helpful" to the jury, it must be that the evidence establishes a causal relationship to a reasonable degree of scientific certainty. *Finn v. Warren Cty., Kentucky*, 768 F.3d 441, 452 (6th Cir. 2014). Finally, note that Dr. Keyes asserts that she would "draw the conclusion in any forum." But, in fact, she has not done so in any forum other than this litigation.[29] The Sixth Circuit "has recognized for some time that expert testimony prepared solely for purposes of litigation, as opposed to testimony flowing naturally from an expert's line of scientific research

[27] Ex. 9, Keyes Dep. 305.

[28] The one relevant study published since Compton suggest a contrary conclusion—that "***medical*** use of opioids as prescribed does not cause opioid use disorder." Ex. 8, Lyerla Report at 2 (citing McCabe, S. E., Veliz, P. T., Boyd, C. J., Schepis, T. S., McCabe, V. V., & Schulenberg, J. E., A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. Drug and Alcohol Dependence, 194, 377–385 (2019)).

[29] Similarly, Dr. Lembke has never used the term "Gateway Effect" in any peer-reviewed scientific journal. Ex. 2, Lembke Dep. 82.

or technical work, should be viewed with some caution." *Johnson v. Manitowoc Boom Trucks, Inc.*, 484 F.3d 426, 434 (6th Cir. 2007).

Similarly, Dr. Gruber admits that the literature on which he relies "are not causal studies"[30] and that when he says these studies "establish[] the link" between opioid use and heroin abuse, he doesn't "mean that to say that these studies are causal evidence of that link."[31] The only other evidence on which he relies to support a causal link between opioid use and heroin abuse is his assertion that there is a correlation between counties to which more opioids were shipped and the rate of mortality from illicit opioids.[32] As set forth in Defendants' *Daubert* Motion to Exclude the Opinions Offered by Jonathan Gruber, Ph.D., this correlation is equally insufficient to prove causation.

And Dr. Lembke does not even try to assert that there is a causal relationship between non-medical opioid use and heroin abuse, stating only that there is a "clear link" between prescription-opioid use and heroin abuse.[33] She acknowledged in her 2016 book that "the relationship between doctors' prescribing patterns and the initiation of heroin use remains unclear,"[34] and her report does not identify any newer evidence that would warrant a change in

[30] Ex. 3, Gruber Dep. 332–333; *see also id.* at 271.

[31] *Id.* at 299.

[32] Gruber Report at 9.

[33] Lembke Report at 84 ("There is a clear link between prescription opioid exposure and subsequent use of heroin and other illicit opioids."). Should Plaintiffs argue that Dr. Lembke opined that prescription-opioid use *causes* heroin abuse, this opinion, too, should be excluded as unreliable for lack of evidentiary support.

[34] Lembke, *Drug Dealer MD* 109 (2016). Dr. Lembke testified that the book was completed two years before it was published. Even so, she does not identify any post-2014 studies that conclude there is a causal connection between prescription-opioid use and heroin use.

her conclusion. She agrees with Dr. Compton's 2016 article, which concluded that "nonmedical prescription opioid use is neither necessary nor sufficient for the initiation of heroin use[35].

Not only do each of the Three Experts fail to identify reliable evidence in support of a causal relationship, each ignores affirmative evidence in the record to the contrary. Dr. Lyerla notes that, "[i]n epidemiology, and in particular for behavioral health conditions, causal relationships, such as the one that the gateway hypothesis suggests, are difficult to substantiate. This is particularly so when the observed conditions and behaviors implicate multiple, overlapping, potentially contributing factors and confounders" (i.e., variables that can cause the observed outcome, even though they are not themselves the subject of study).[36] The 16 articles concern retrospective observational studies, which by definition can only "suggest association, not causality," because they examine historical data and cannot control for important contributing factors and confounders.[37] The Muhuri article[38] relied upon by the Experts, he points out, concluded that even most ***non-medical*** users of prescription opioids "do not progress to heroin use."[39] Also telling is the fact that, although Dr. Keyes said she considered the most recent data (but cited none), a 2019 study, which actually looked at ***medical use*** of prescription

[35] Ex. 2, Lembke Dep. 141.

[36] Ex. 8, Lyerla Report at 5.

[37] *Id.* at 2.

[38] Muhuri, P. K., Gfroerer, J. C., & Davies, M. C. (2013). CBHSQ Data Review: Associations of nonmedical pain reliever use and initiation of heroin use in the United States. Rockville, MD: Substance Abuse and Mental Health Services Administration (SAMHSA). Retrieved from https://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm. The article was published by SAMHSA, where Dr. Lyerla worked.

[39] *Id.*

opioids, "suggest[s] that medical use of opioids as prescribed does not cause opioid use disorder."[40]

Given that their opinions do not support a conclusion of causation, the Experts should not be allowed to opine instead that there is a correlation between non-medical prescription opioid use and heroin abuse. That is not a relevant question in this litigation, in which the only relevant question is one of causation. Accordingly, an expert who cannot opine to a reasonable degree of scientific certainty that an association between two events is causal does not have "helpful" or "relevant" testimony to offer as a matter of law. Plaintiffs cannot recover heroin-related costs based on a connection that is merely temporal, or plausible, or suggestive. "A temporal relationship by itself, provides no evidence of causation." *In re Breast Implant Litig.*, 11 F.Supp.2d 1217, 1232 (D. Colo. 1998) (citing cases).

V. PLAINTIFFS' GATEWAY HYPOTHESIS IS FUNDAMENTALLY MISLEADING

Daubert and its progeny established the Court as a "gatekeeper" because "[e]xpert evidence can be both powerful and quite misleading because of the difficulty in evaluating it. Because of this risk, the judge in weighing possible prejudice against probative force … exercises more control over experts than over lay witnesses." *Daubert*, 509 U.S. 579 at 595. "Federal judges must therefore exclude proffered scientific evidence under Rules 702 and 403 unless they are convinced that [the evidence] speaks clearly and directly to an issue in dispute in the case, and that it will not mislead the jury." *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1321 n.17 (9th Cir. 1995).

[40] Ex. 8, Lyerla Report at 2.

As noted above, the Three Experts rely on studies that examined a population of individuals who used prescription opioids not because a doctor prescribed them and not to alleviate pain, but for "the experience or feeling that they caused." It would mislead the jury to admit testimony based on these studies. When Plaintiffs are seeking to recover damages that arise from persons who allegedly became addicted to opioids prescribed by their doctors, it is fundamentally misleading to rely on evidence about persons who are not known ever to have received a doctor's prescription for opioids and who instead abused these medications.

But beyond that, all of the testimony opining on an unreliable "link" between Defendants and the heroin trade would unduly prejudice the Defendants. Courts should "exercise greater care" where the expert's testimony presents a risk of "subliminally inciting or confusing the jury." *United States v. Green*, 548 F.2d 1261, 1270 (6th Cir. 1977) (reversing convictions for illegal drug manufacturing after district court admitted DEA expert who provided prejudicial background about the illegal drug trade).

CONCLUSION

The Court should exclude the testimony of the three experts about the "gateway" hypothesis because their opinions are unreliable and misleading. The experts rely on evidence regarding an irrelevant population of opioids users and draw conclusions from those studies that their own authors were unwilling to draw. Accordingly, *Daubert* requires that these opinions be deemed inadmissible.

Dated: June 28, 2019 Respectfully submitted,

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[41] Teva Pharmaceutical Industries Ltd., Allergan plc, and Mallinckrodt plc are respectively an Israeli corporation, Irish holding company, and Irish company that are not subject to and contest personal jurisdiction for the reasons explained in their pending motions to dismiss for lack of personal jurisdiction; they are specially appearing to join this motion as a result of the Court's deadline to file dispositive and Daubert motions, and, thus, they do not waive and expressly preserve their pending personal jurisdiction challenges.

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CERTIFICATE OF SERVICE

I, Ashley W. Hardin, hereby certify that the foregoing document was served on all counsel of record via the Court's ECF system.

/s/ Ashley W. Hardin
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